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ORIGINAL ARTICLE

Comparisons of pathologic findings and outcomes of gastric cancer patients younger and older than 40: a propensity score matching study in a single center of Korea

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Key words

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Abstract

Background and Aim: Gastric cancer (GC) is one of the most common cancers worldwide, with a high incidence rate in Korean men. However, comparative studies are scarce on the pathologic findings and treatment effects of GC in patients aged less than 40 years. We evaluated the characteristics and pathologic findings of GC patients aged younger and older than 40 years.

Methods: We retrospectively analyzed 2307 patients diagnosed with GC between January 2010 and May 2018. Eighty-eight (3.8%) and 2219 (96.2%) patients were younger and older than 40 years, respectively. The patients were divided into younger ($n = 70$) and older ($n = 62$) age groups through propensity matching.

Results: Overall, compared to the younger group, the older group ($n = 2219$) had a significantly higher proportion of male patients (66.7% *vs* 39.8%; $P < 0.001$) and patients who underwent endoscopic submucosal dissection (ESD) (2.3% *vs* 23.1%; $P < 0.001$). However, young patients more often underwent operations compared to older patients (78.4% *vs* 60.1%; $P = 0.001$). In the propensity-matched group, older patients more often showed differentiated carcinoma, including well-differentiated (5.7% *vs* 11.3%) and moderately differentiated (1.4% *vs* 32.3%). However, younger patients more often showed signet ring cell carcinoma (SRC) (70.0% *vs* 25.8%). In multivariate analysis, *Helicobacter pylori* infection (odds ratio, 12.643; 95% confidence interval, 1.068–1449.665; $P = 0.044$) independently correlated with SRC risk.

Conclusions: Patients below 40 years were more likely to undergo surgery compared to ESD, and pathologic findings were more common in SRC. Therefore, more active screening and *H. pylori* eradication are needed even in patients aged less than 40 years.

Introduction

According to estimates from the International Agency for Research on Cancer (IARC), gastric cancer (GC) is an important carcinoma, ranking fifth in incidence and third among causes of cancer deaths in 2018.[1] In addition, the Korea Central Cancer Registry in 2016 reported that GC was the most commonly diagnosed cancer, especially in men (crude rate [CR] 80.3 per 100 000).[2] Owing to this high incidence rate, since its inception in 1999, the National Cancer Screening Program in Korea provides gastroscopy every 2 years for healthy population aged over 40 years. The incidence of GC decreased by 5.4 (annual percentage change [APC]) in men and 4.5 (APC) in women between 1999 (start of screening) and 2016; however, the rate of GC in men in Korea was the highest in 2016.[2] In addition, GC occurs most commonly in patients in their 50s and 70s,[3–5] and it is difficult to predict GC in young patients (<40 years of age) because GC is detected in 2.4–6.2% of these patients, who are not included in the screening.[4,6–8]

In the United States, the incidence of GC tends to increase in patients aged <40 years.[9] Several studies have reported that GC occurring in young patients has poor differentiation, diffuse cancer infiltration, and a poor prognosis.[10–12] However, other studies have reported the same or better prognosis for younger patients with GC.[8,13–15] Therefore, the prognosis of GC in relatively young patients is controversial.

There is a lack of research addressing the risk of GC in patients <40 years of age, their characteristics, and whether endoscopy should be performed before the age of 40. Therefore, this study investigated the pathological characteristics and risk factors of patients younger and older than 40 years of age through propensity matching.

Methods

Patients. From January 2010 to May 2018, a total of 2844 patients were diagnosed with GC at Haeundae Paik Hospital, Inje

University, in Busan, Korea. Of these, 537 patients were excluded based on the following exclusion criteria: (i) patients who were diagnosed with other diseases such as gastrointestinal stromal tumor (GIST), carcinoid tumor, schwannoma, and leiomyosarcoma, and (ii) patients whose pathologic data were not available (n = 500). Among them, 88 (3.8%) and 2219 (96.2%) patients were ≤40 and >40 years of age, respectively.

To evaluate the long-term follow-up outcomes and compare patients younger and older than 40 years, we divided the patients into younger (≤40 years, n = 70) and older (>40 years, n = 70) age groups by propensity matching. We excluded eight patients meeting the following exclusion criteria: (i) no available clinical data or clinical records, (ii) gastric metastasis due to other primary-originated cancer, and (iii) no pathological findings. In the propensity-matching analysis, the covariates included gender and treatment modality. In summary, the propensity analysis included a total of 132 matched patients, including 70 younger and 62 older patients, diagnosed with GC between 2010 and 2018, who were included in further analyses of pathologic findings and outcomes (Fig. 1).

This study was conducted under the ethical guidelines of the 1975 Declaration of Helsinki and approved by the institutional review board of Haeundae Paik Hospital.

Definition of GC and staging. GC is clinically classified as early or advanced.[16] The World Health Organization (WHO) defines early gastric carcinoma (EGC) as invasive carcinoma of the stomach up to the submucosal layer, regardless of nodal status,[17] while advanced gastric carcinoma (AGC) refers to invasive carcinoma invading the muscularis propria or beyond.[18] According to Borrmann's classification, the gross appearance of AGC can be divided into polypoid (type I), fungating (type II), ulcerating (type III), and diffusely infiltrating (type IV, linitis plastica) cancers.[19] Gastric adenocarcinoma stage was determined according to the eighth edition of the American Joint Committee on Cancer staging.[20]

Lesion locations. GC arises in gastric epithelial cells that are heterogeneous and distinguishable histologically in three gastric regions: the cardia, corpus fundus, and antrum pylorus.[21] Therefore, we defined the lesion locations as antrum, angle, corpus, cardia, or multiple. If concurrent lesions were observed at the time of diagnosis, the largest or GC lesions were analyzed as the major lesions.

Pathologic findings. The 2010 WHO classification is commonly used to describe major histologic patterns of GCs as adenocarcinoma (tubular, papillary, or mucinous adenocarcinoma), signet ring cell carcinoma (SRC), poorly cohesive carcinoma, and uncommon histologic variants.[17] The classification often coexists with other less predominant histologic patterns and is based on the predominant histologic patterns of the carcinoma. In addition, *Helicobacter pylori* infection was confirmed based on positive urease or urea breath test findings and/or on the pathological confirmation at the time of cancer diagnosis.

Treatment modalities

Endoscopic submucosal dissection. Endoscopic submucosal dissection (ESD) is the most common treatment option for gastrointestinal neoplasm, including EGC.[22,23] ESD was performed in patients with absolute indications, including intramucosal differentiated-type adenocarcinoma measuring <2 cm without ulceration, and also in those with expanded indications. The expanded indications included (i) mucosal cancer without ulcer findings,

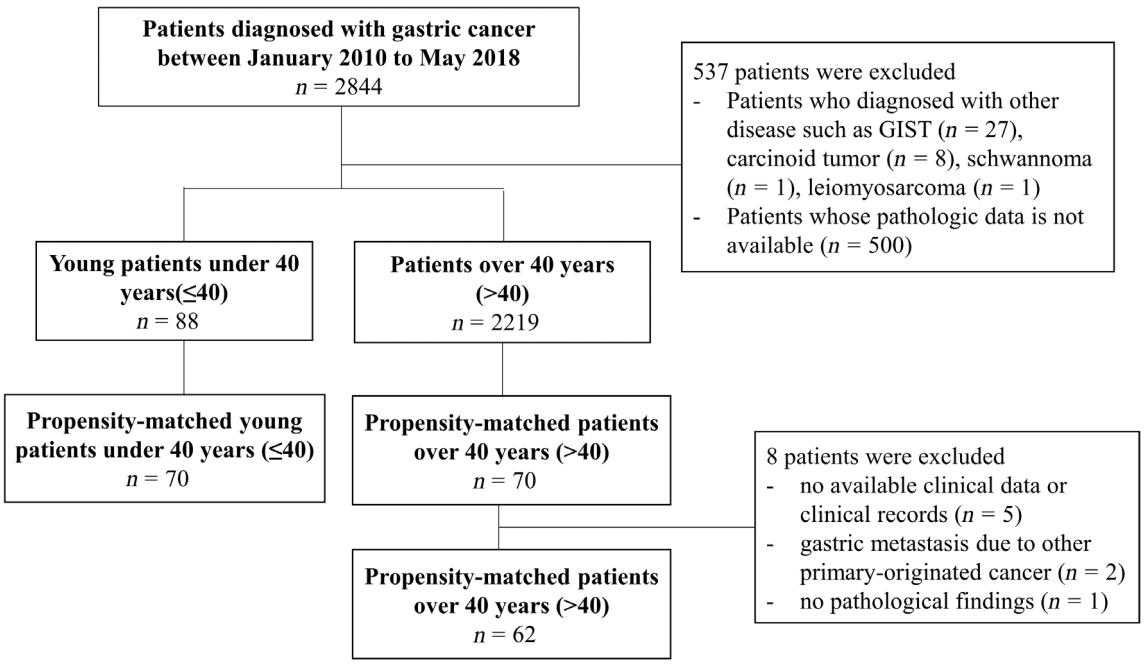

Figure 1 Flowchart of patients enrollment.

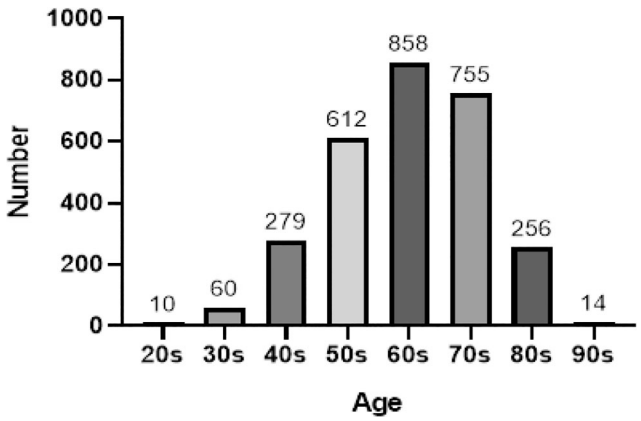

Figure 2 Distribution of gastric cancer patients over 9 years by age.

irrespective of tumor size; (ii) mucosal cancer with an ulcer ≤3 cm in diameter; and (iii) minimal (≤500 μm from the muscularis mucosa) submucosal invasive cancer ≤3 cm in size.[24,25] The shape and margin of these lesions were determined, and the endoscopic procedures were performed using a single-channel endoscope (GIF H260; Olympus, Tokyo, Japan). Using argon plasma coagulation, the lesion boundary was marked with dotted lines. Isotonic saline with dilute epinephrine (1:10 000) was then injected into the submucosal layer to elevate the lesion. For ESD, a circumferential incision was made around the lesion, which was dissected using an insulated tipped knife (or dual knife; Olympus). For sedation, 3–5 mg of midazolam was administered intravenously. All patients were monitored for cardiopulmonary functions.

Operations. Surgical treatment was performed when the GC was diagnosed as AGC or when lymph node (LN) enlargement was observed by abdominal pelvis computed tomography imaging. The operations included subtotal or total gastrectomy, with LN dissection performed by an experienced surgeon. The extent of resection was determined according to the cancer location and size, and lymphectomy was performed according to the guidelines of the Japanese Research Society for GC. However, some patients had different types of surgical procedures done such as bypass surgery, primary repair, or gastrectomy for palliative purposes due to mass bleeding, perforation, or intestinal obstruction. Moreover, additional surgery was performed in patients with incomplete resection after ESD, lymphovascular invasion, or submucosal invasion over T1a (>500 μm); therefore, we categorized patients who underwent ESD and additional surgery into a "both" group.

Chemotherapy. In AGC, adjuvant chemotherapy was administered before or after surgery, with palliative chemotherapy provided if surgery was difficult. Chemotherapy was administered based on the National Comprehensive Cancer Network guidelines in consultation with oncologists and surgeons.

Statistical analysis. Variables were expressed as medians and interquartile range (IQR) or as numbers and percentage. The baseline characteristics were compared using independent Student's *t*-test or Mann–Whitney test for continuous variables and χ^2 test or Fisher's exact test for categorical variables, as appropriate. We compared the baseline characteristics and treatment modalities between young (≤40 years) and older (>40 years) patients. In addition, we also assessed the differences according to the propensity analysis of 132 pairs of young and older patients. The independent predictors of SRC and mortality in the propensity-matched analysis were analyzed by logistic regression. The odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated. In addition, the overall cumulative risk rates of survival following ages were determined using the Kaplan–Meier method and compared using log-rank tests.

Table 1 Baseline characteristics of study subjects

Variables	Total (n = 2307)	Young patients (≤40) (n = 88, 3.8%)	Patients over 40 years (>40) (n = 2219, 96.2%)	*P*-value*
Male sex	1514 (65.6)	35 (39.8)	1479 (66.7)	<0.001
Median age	64 (56–73)	37 (33–39)	65 (57–73)	<0.001
Mortality	96 (4.2)	4 (4.5)	92 (4.2)	0.861
Treatment modality				
ESD	515 (22.3)	2 (2.3)	513 (23.1)	<0.001
Surgery	1403 (60.8)	69 (78.4)	1334 (60.1)	0.001
Both (ESD and surgery)	61 (2.6)	1 (1.1)	60 (2.7)	0.369
Chemotherapy or no treatment	468 (20.3)	36 (40.9)	432 (19.5)	<0.001
Pathologic findings				<0.001
Well differentiated	567 (24.6)	3 (3.4)	564 (25.4)	
Moderately differentiated	626 (27.2)	1 (1.1)	625 (28.2)	
Poorly differentiated	486 (21.1)	17 (19.3)	469 (21.2)	
Signet ring cell	419 (18.2)	52 (59.1)	367 (16.6)	
Others†	161 (7.0)	11 (12.5)	150 (6.8)	
Helicobacter pylori infection (n = 1664)	448 (26.9)	31 (52.5)	417 (26.0)	<0.001

**P*-value for comparing patients with young group and patients over 40 years.
†Mucinous carcinoma, adenosquamous carcinoma.
Data are expressed as median (interquartile range, IQR) or *n* (%).
ESD, endoscopic submucosal dissection.

Table 2 Baseline characteristics of study subjects in propensity-matched analysis of 132 patients

Variables	Young patients (≤40) ($n = 70$, 53.0%)	Patients over 40 years (>40) ($n = 62$, 47.0%)	*P*-value*
Male sex	30 (42.9)	28 (45.2)	0.790
Mean age	37 (33–39)	67 (58–78)	
Treatment modality			
ESD	2 (2.9)	2 (3.2)	1.000
Surgery	51 (72.9)	49 (79.0)	0.409
Both (ESD and surgery)	1 (1.4)	1 (1.6)	1.000
Chemotherapy or no treatment	18 (25.7)	12 (19.4)	0.384
Methods of operation			0.762
STG with BI	3 (5.8)	3 (5.9)	
STG with BII	41 (78.8)	38 (74.5)	
TG with EJstomy	8 (15.4)	9 (17.6)	
Others†	0 (0)	1 (2.0)	
Purpose of operation			1.000
Curative	51 (96.2)	49 (96.1)	
Palliative	2 (3.8)	2 (3.9)	
Synchronous lesion	2 (2.9)	1 (1.6)	1.000
Lab findings			
Hemoglobin	12.6 (10.6–14.3)	13.1 (11.3–14.6)	0.318
CEA	2.4 (1.1–5.2)	1.6 (0.8–2.9)	0.044
Family history	14 (20.0)	4 (6.5)	0.024
Family member affected			
Father	6 (42.9)	1 (25.0)	0.238
Mother	6 (42.9)	1 (25.0)	
Siblings	1 (7.1)	2 (50.0)	
Both	1 (7.1)	0 (0)	
Underlying disease			
Hypertension	0 (0)	23 (37.1)	<0.001
Diabetes	0 (0)	14 (22.6)	<0.001
Other‡	2 (2.9)	27 (43.5)	<0.001

**P*-value for comparing patients with young group and patients over 40 years.
†Open and closure.
‡Cardiovascular disease, tuberculosis, chronic obstructive pulmonary disease, viral hepatitis.
Data are expressed as *n* (%).
CEA, carcinoembryonic antigen; ESD, endoscopic submucosal dissection; STG with BI, subtotal gastrectomy with billroth I; TG with EJstomy, total gastrectomy with esophagojejunostomy.

Data analysis was performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corporation, Armonk, NY, USA). *P*-values <0.05 were considered statistically significant. The graphs of the distributions of patients with GC and their pathologic findings were drawn using GraphPad Prism 6.0 (GraphPad Software, La Jolla, CA, USA).

Results

Baseline patient characteristics. From January 2010 to May 2018, 2844 patients were diagnosed with GC at Haeundae Paik Hospital. Among these patients, 88 (3.8%) were ≤40 years of age and 2219 (96.2%) were older than 40 years. Figure 2 shows the distributions of GC diagnosed for each generation during the 9-year study period. A total of 2307 patients with GC were analyzed. Their baseline characteristics are shown in Table 1. In this study, 65.6% of the patients were male, and a higher number of patients >40 years were male compared to the younger age group (39.8% *vs* 66.7%; $P < 0.001$). The average age of the study subjects was 64 years (IQR, 56–73 years).

The treatment modalities differed significantly between the groups younger than and older than 40 years of age. Compared to younger patients, more older patients underwent ESD (2.3% *vs* 23.1%; $P < 0.001$), while more younger patients underwent surgery (78.4% *vs* 60.1%; $P = 0.001$). In addition, SRC (59.1% *vs* 16.6%; $P < 0.001$) and *H. pylori* infection rate (52.5% *vs* 26.0%; $P < 0.001$) were significantly higher in patients ≤40 years compared to patients >40 years (Table 1).

Propensity-matching analysis. To compare patients above and below 40 years of age, young ($n = 70$) and older ($n = 62$) patients were selected through propensity matching. Absolute standard difference (ASD) graphs before and after propensity score matching are shown in Figure S1. The results of the analysis of their baseline characteristics are shown in Table 2. The two age groups showed significant differences in underlying diseases (hypertension, 0% *vs* 37.1%; $P < 0.001$ and diabetes, 0% *vs* 22.6%; $P < 0.001$) but not in sex or treatment modality (all $P > 0.05$).

The two age groups showed significant differences in tumor location, stage, and carcinoembryonic antigen (CEA) level. Compared to the older patients, younger patients showed higher occurrences of corpus, cardia, and multiple lesion locations (corpus, 58.6% *vs* 33.9%; cardia, 5.7% *vs* 4.8%; multiple lesions, 4.3% *vs* 3.2%; $P = 0.010$) and rates of stage IA or stage IV disease (stage IA, 50.0% *vs* 33.9%; stage IV, 25.7% *vs* 14.5%; $P = 0.018$). In addition, in the young group, the CEA level was higher than in the older group (2.4 [1.1–5.2] *vs* 1.6 [0.8–2.9]; $P = 0.044$). The proportion of patients with a family history was also significantly higher in the young patient group (20.0% *vs* 6.5%; $P = 0.024$). However, compared to those ≤40 years of age, the recurrence rate was higher in those >40 years of age (2.9% *vs* 14.5%; $P = 0.016$). The mortality rates did not differ between the two groups (Tables 2 and 3). The pathologic findings and outcomes of 88 patients under the age of 40 before propensity matching are presented in Table S1.

Pathologic findings in the 132 propensity-matched patients. The young patients showed a significantly higher incidence of SRC (70.0% *vs* 25.8%; $P < 0.001$) and *H. pylori* infection (68.4% *vs* 4.9%; $P < 0.001$). The older patients showed a higher occurrence of differentiated-type adenocarcinoma (well differentiated, 5.7% *vs* 11.3%; moderately differentiated, 1.4% *vs* 32.3%; poorly differentiated (PD), 18.6% *vs* 29.0%; $P < 0.001$; Table 3 and Fig. 3).

Risk factors of SRC in the 132 propensity-matched patients. The results of univariate and multivariate logistic regression analysis of SRC risk factors are shown in Table 4. The univariate logistic regression analysis showed that

Table 3 Comparison of pathologic findings, clinical stage, and outcome between young patients and patients over 40 years in propensity-matched analysis of 132 patients

Variables	Total ($n = 132$)	Young patients (≤40) ($n = 70$, 53.0%)	Patients over 40 years (>40) ($n = 62$, 47.0%)	*P*-value*
Pathology findings				<0.001
Well differentiated	11 (8.3)	4 (5.7)	7 (11.3)	
Moderately differentiated	21 (15.9)	1 (1.4)	20 (32.3)	
Poorly differentiated	31 (23.5)	13 (18.6)	18 (29.0)	
Signet ring cell	65 (49.2)	49 (70.0)	16 (25.8)	
Others†	4 (3.0)	3 (4.3)	1 (1.6)	
Helicobacter pylori infection ($n = 60$)	15 (25.0)	13 (68.4)	2 (4.9)	<0.001
Classification of stomach cancer				0.679
EGC	60 (45.5)	33 (47.1)	27 (43.5)	
AGC	72 (54.5)	37 (52.9)	35 (56.5)	
Location				0.010
Antrum	51 (38.6)	17 (24.3)	34 (54.8)	
Angle	7 (5.3)	5 (7.1)	2 (3.2)	
Corpus	62 (47.0)	41 (58.6)	21 (33.9)	
Cardia	7 (5.3)	4 (5.7)	3 (4.8)	
Multiple	5 (3.8)	3 (4.3)	2 (3.2)	
Stage				0.018
IA	56 (42.4)	35 (50.0)	21 (33.9)	
IB	11 (8.3)	3 (4.3)	8 (12.9)	
IIA	10 (7.6)	6 (8.6)	4 (6.5)	
IIB	7 (5.3)	3 (4.3)	4 (6.5)	
IIIA	4 (3.0)	1 (1.4)	3 (4.8)	
IIIB	9 (6.8)	1 (1.4)	8 (12.9)	
IIIC	5 (3.8)	3 (4.3)	2 (3.2)	
IV	27 (20.5)	18 (25.7)	9 (14.5)	
Unknown	3 (2.3)	0 (0)	3 (4.8)	
Recurrence	11 (8.3)	2 (2.9)	9 (14.5)	0.016
Mortality	26 (19.7)	13 (26.5)	13 (28.9)	0.798

**P*-value is for comparing young patients and patients over 40 years.
†Mucinous carcinoma and adenosquamous carcinoma.
Data are expressed as median (interquartile range, IQR) or *n* (%).
AGC, advanced gastric cancer; EGC, early gastric cancer.

male sex (OR, 0.448; 95% CI, 0.222–0.904; $P = 0.025$), age <40 years (OR, 6.618; 95% CI, 3.089–14.175; $P < 0.001$),

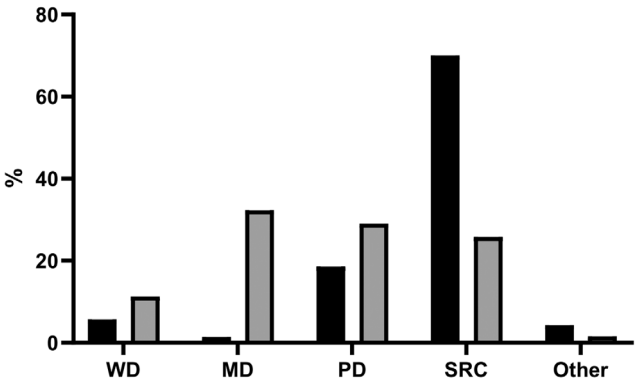

Figure 3 Pathologic findings between younger patients and patients over 40 years in propensity-matched analysis of 132 patients. ■, ≤40 years; □, >40 years.

H. pylori infection (OR, 14.393; 95% CI, 2.857–72.507; $P = 0.001$), and cancer location in the corpus (OR, 3.579; 95% CI, 1.643–7.798; $P = 0.001$) were significantly associated with SRC. Among these variables, *H. pylori* infection was associated with a significantly increased risk in the multivariate analysis (OR, 12.643; 95% CI, 1.068–1449.665; $P = 0.044$; Table 4). In addition, as a result of analyzing the risk factors for SRC in 2307 GC patients, age <40 (OR, 5.348; 95% CI, 3.063–9.338; $P < 0.001$) and *H. pylori* infection (OR, 1.810; 95% CI, 1.374–2.385; $P < 0.001$) were significant independent factors in multivariate logistic regression analysis. Additionally, the data showed male gender was negatively associated with SRC (OR, 0.353; 95% CI, 0.271–0.459; $P < 0.001$; Table S2).

Risk factors for mortality in 132 propensity-matched patients. Univariate logistic regression analysis showed a significant increase in the risk of mortality in patients who were elderly (>70 years of age; OR, 2.687; 95% CI, 1.063–6.797; $P = 0.037$), underwent chemotherapy or no treatment (OR, 10.514; 95% CI, 3.987–27.729; $P < 0.001$), with PD adenocarcinoma (OR, 2.766; 95% CI, 1.151–6.649; $P = 0.023$),

Table 4 Risk factors of signet ring cell carcinoma in propensity-matched analysis of 132 patients

	Univariate analysis		Multivariate analysis	
Variable	*P*-value	OR (95% CI)	*P*-value	Adjusted OR (95% CI)
Male sex	0.025	0.448 (0.222–0.904)	0.960	0.966 (0.247–3.770)
Younger patients (≤40 years)	<0.001	6.618 (3.089–14.175)	0.619	1.549 (0.275–8.724)
Helicobacter pylori infection	0.001	14.393 (2.857–72.507)	0.044	12.643 (1.068–1449.665)
Synchronous lesion	0.584	1.969 (0.174–22.260)		
Location of cancer				
Antrum		1.0 (ref)		1.0 (ref)
Angle	0.275	2.444 (0.492–12.148)	1.000	0.000 (0.000)
Corpus	0.001	3.579 (1.643–7.798)	0.161	2.617 (0.681–10.055)
Cardia	0.697	1.375 (0.277–6.833)	0.999	0.000 (0.000)
Broad or linitis plastica	0.500	0.458 (0.048–4.416)	0.999	0.000 (0.000)
Laboratory findings				
Hemoglobin	0.175	1.098 (0.959–1.258)		
CEA	0.269	0.985 (0.959–1.012)		
Family history of gastric cancer	0.153	2.145 (0.753–6.110)		
Family member affected				
Father		1.0 (ref.)		
Mother	0.579	1.875 (0.204–17.269)		
Siblings	0.779	1.500 (0.089–25.392)		
Both	1.000	1 211 606 132 (0.000)		

CEA, carcinoembryonic antigen; CI, confidence interval; OR, odds ratio.

Table 5 Risk factors of mortality in propensity-matched analysis of 132 patients

	Univariate analysis		Multivariate analysis	
Variable	*P*-value	OR (95% CI)	*P*-value	Adjusted OR (95% CI)
Male sex	0.259	1.644 (0.694–3.894)	0.627	1.314 (0.437–3.953)
Younger patients (≤40 years)	0.730	0.860 (0.364–2.028)	0.884	0.911 (0.260–3.186)
Elderly patients (≥70 years)	0.037	2.687 (1.063–6.797)	0.997	1.004 (0.124–8.143)
Treatment modality				
ESD	0.999	0.000 (0.000)		
Surgery	<0.001	0.111 (0.043–0.288)		
Chemotherapy or no treatment	<0.001	10.514 (3.987–27.729)		
Pathologic findings				
Well differentiated	0.999	0.000 (0.000)		
Moderately differentiated	0.783	0.859 (0.292–2.528)		
Poorly differentiated	0.023	2.766 (1.151–6.649)	0.112	2.433 (0.813–7.279)
Signet ring cell carcinoma	0.165	0.537 (0.223–1.292)		
Others†	0.153	4.333 (0.581–32.328)		
Helicobacter pylori infection	0.835	0.835 (0.154–4.540)		
Synchronous lesion	0.556	2.080 (0.181–23.860)		
Stage				
I	1.0	1.0 (ref)	1.0	1.0 (ref)
II, III	0.006	9.630 (1.919–48.328)	0.046	9.736 (1.037–91.368)
IV	<0.001	40.625 (8.212–200.968)	0.010	24.872 (2.171–284.940)
EGC in pathologic finding	1.0	1.0 (ref.)	1.0	1.0 (ref)
AGC	0.001	8.918 (2.524–31.512)	0.898	0.875 (0.114–6.701)
Location of cancer				
Antrum	1.0	1.0 (ref)		
Angle	0.999	0.000 (0.000)		
Corpus	0.146	0.481 (0.180–1.289)		
Cardia	0.078	4.333 (0.848–22.134)		
Broad or linitis plastica	0.426	2.167 (0.323–14.524)		
Laboratory findings				
Hemoglobin	<0.001	0.706 (0.589–0.845)	0.116	0.840 (0.676–1.044)
CEA	0.236	1.010 (0.993–1.027)		
Family history of gastric cancer	0.772	1.195 (0.358–3.985)		
Family member affected				
Father	1.0	1.0 (ref)		
Mother	0.522	2.400 (0.165–34.928)		
Siblings	0.501	3.000 (0.122–73.642)		
Both	1.000	0.000 (0.000)		

†Mucinous carcinoma and adenosquamous carcinoma.

AGC, advanced gastric cancer; CEA, carcinoembryonic antigen; CI, confidence interval; EGC, early gastric cancer; ESD, endoscopic submucosal dissection; OR, odds ratio.

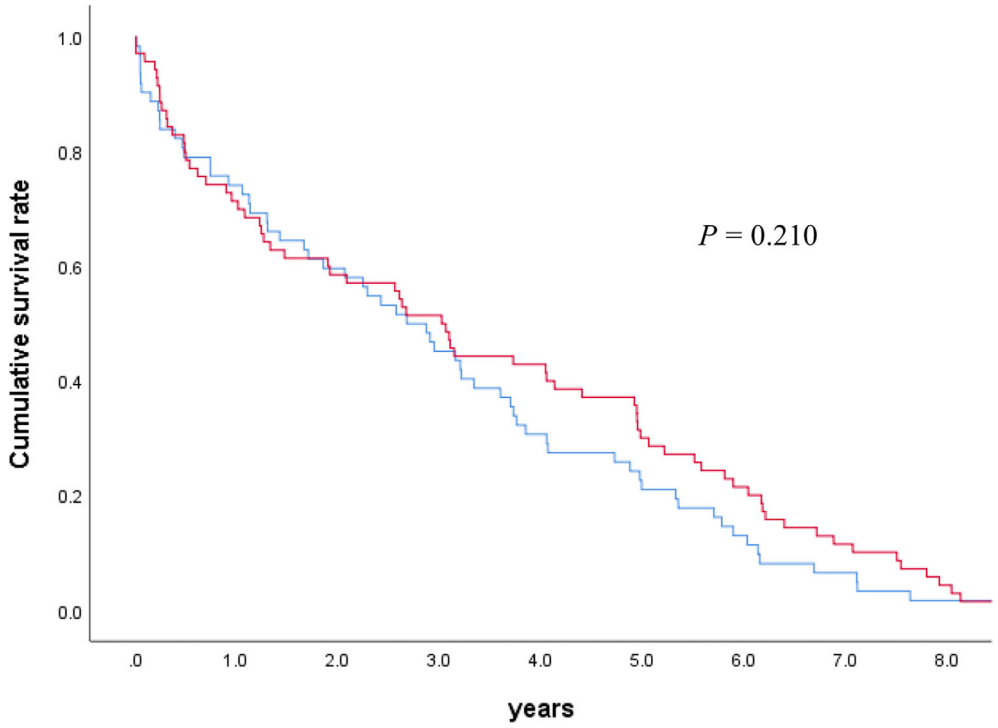

Figure 4 Cumulative survival rate in case–control-matched group (Kaplan–Meier graph). ⌐¬, Elderly patients (>40 years); ⌐¬, younger patients (≤40 years).

with stage II/III disease (OR, 9.630; 95% CI, 1.919–48.328; $P = 0.006$), with stage IV disease (OR, 40.625; 95% CI, 8.212–200.968; $P < 0.001$), and had AGC instead of EGC (OR, 8.918; 95% CI, 2.524–31.512; $P = 0.001$). However, surgery (OR, 0.111; 95% CI, 0.043–0.288; $P < 0.001$) and high hemoglobin levels (OR, 0.706; 95% CI, 0.589–0.845; $P < 0.001$) were significantly associated with decreased mortality. Among these variables, stage II/III disease (OR, 9.736; 95% CI, 1.037–91.368; $P = 0.046$) and stage IV disease (OR, 24.872; 95% CI, 2.171–284.940; $P = 0.010$) were associated with significantly increased mortality in the multivariate analysis (Table 5).

The median survival duration was 2.89 years. The log-rank curves did not show significant differences in survival rates between the ≤40 and >40 year age groups in the case–control matching group ($P = 0.210$) (Fig. 4). In addition, analysis of the risk factors for recurrence also showed no significant differences in these age groups ($P > 0.05$). However, in multivariate logistic regression analysis, PD adenocarcinoma was an important risk factor for recurrence (OR, 9.583; 95% CI, 1.752–52.406; $P = 0.009$; Table S3).

Discussion

Although the National Cancer Screening Program provides gastroscopy every 2 years for healthy people above 40 years of age, the incidence of GC in Korea remains high[2] and approximately 3.55% cases of GC occur in young patients.[26] Consistent with previous reports, this study found that 3.8% (88 of 2307) patients with GC were ≤40 years of age. Moreover, these young patients also had a higher SRC rate compared to patients >40 years of age and they were significantly more likely to receive surgical treatment instead of ESD. Moreover, propensity-matched analysis showed significantly higher rates of pathologic findings in SRC (70.0% *vs* 25.8%), *H. pylori* infection (68.4% *vs* 4.9%), and cancer mainly occurring in the corpus (58.6% *vs* 33.9%). There were also relatively many cases of stage IV (25.7% *vs* 14.5%) disease in the younger group. However, there was no significant difference in mortality between groups. The most significant risk factor for SRC was the accompanying *H. pylori* infection. In addition, when the risk factors for SRC were analyzed in all 2307 adult patients diagnosed with GC, it was confirmed that young patients under the age of 40 and with *H. pylori* infection showed a significant relationship with SRC (Table S2). Therefore, the risk of developing SRC may be higher if accompanied by *H. pylori* infection in young patients.

Generally, the antrum and lesser curvature of the stomach were the most common locations of GCs resected by ESD or surgery.[27–29] This may be because the gastric carcinogenesis cascade (atrophy–metaplasia–dysplasia–adenocarcinoma sequence; Correa's cascade) due to *H. pylori* infection and atrophic gastritis changes mainly proceed along the lesser curvature from the antrum to the corpus.[30,31] However, there are reports in young patients with GC in whom cancer is detected in the antrum but more often in the body.[32,33] Lee *et al.*[32] observed GC in the body in 66.3% of young patients with GC (≤40 years of age). Another Japanese study found GC in the middle side of stomach in 51.5% of younger patients.[33] Similarly, in our study, more cancers occurred in the corpus in younger patients with GC

compared to older GC patients (58.6% *vs* 33.9%) and often in the corpus than in the antrum (58.6% *vs* 24.3%). Kim *et al.*[34] reported that EGC with PD or SRC occurred more commonly in the vertical middle third and transverse anterior or posterior wall compared to other lesions. In addition, another study comparing Korean and American cohorts reported that undifferentiated cancer occurred more frequently in the upper and middle thirds than in the lower third.[35] Thus, younger patients with GC may be affected by other carcinogenic pathways compared to older patients; however, further studies are needed.

Regarding the pathologic findings in this study, SRC was the most common finding in patients with GC aged ≤40 years compared to patients >40 years. Moreover, many patients had stage IV disease at the time of initial diagnosis. Many previous studies have shown similar results, with undifferentiated types of GC in young patients[33] and diffuse-type or PD/SRC reported in other studies of young patients with GC.[36–38] Undifferentiated and diffuse-type GC generally originate from foveolar cells of the gastric fundic glands, while differentiated GC mainly originates from metaplastic mucosa.[33,39] Therefore, undifferentiated-type GC may be more prevalent in young patients with relatively low progression of atrophic gastritis. Furthermore, undifferentiated GC occurs more often with LN invasion; thus, the advanced form of GC may be more common.[39] Isik *et al.*[40] reported a higher rate of metastatic disease in patients ≤40 years of age than in patients aged >40 years (60% *vs* 32.3%). Takatsu *et al.*[33] also reported that LN metastasis was common in young patients with GC but with similar or relatively good overall survival. In the present study, the difference in mortality was not significant in the propensity-matched patients, and recurrence was more common in those >40 years of age. This is likely because younger patients have fewer comorbidities and are more likely to respond to treatment because of their generally better condition.[41] Therefore, caution is necessary because there are relatively many cases of stage IV disease in young patients with GC.

Since its discovery in 1983, *H. pylori* has been reported as an important risk factor for GC.[42,43] A recent Korean study reported a lower incidence of metachronous GC and improved gastric atrophy in patients with EGC treated for *H. pylori* compared to those in patients who received placebo.[44] Choi *et al.*[45] also reported that treatment for *H. pylori* eradication reduced the risk of GC in *H. pylori*-infected patients with a family history of GC among first-degree relatives. In addition, in a study of healthy subjects undergoing check-ups, Park *et al.*[46] found that *H. pylori* infection was a significant risk factor for precancerous lesions in patients aged <40 years. Several studies have reported the benefits of *H. pylori* eradication in young patients aged <40 years. This suggests that the protective effect against GC is better for younger patients than for older patients with atrophic gastritis, as the prevalence of atrophic gastritis is low in patients <40 years of age.[47,48] Therefore, the results of this study confirm that young patients (≤40 years of age) infected with *H. pylori*, which plays an important role in the occurrence of diffuse GC, must receive treatment.

The present study classified patients with GC according to age (>40 and ≤40 years) and investigated the effect of sex and treatment modalities. The pathologic and clinical findings in these patients were also analyzed through propensity-matching analysis. The results revealed that *H. pylori* infection was the most important risk factor for SRC in patients ≤40 years of age. Furthermore, the propensity-matching analysis showed no difference in mortality rates between the age groups, although a higher occurrence of SRC was observed in patients ≤40 years of age. However, this study has several limitations. First, this retrospective study was conducted at a single center. We could not match all covariates such as comorbidities with propensity-matching analysis due to the large difference in number between the two groups (88 patients and 2219 patients) and missing data. And we could not use strict ASD criteria. However, it has the advantage of evaluating patients over 9 years and comparatively analyzing them through propensity matching. Second, comparison with patients without GC was not performed, and selection bias was possible as there were relatively few patients ≤40 years of age compared to all patients. Lastly, it was difficult to compare detailed endoscopic findings and *H. pylori* eradication rates. Although there were records of cancer findings, in cases where endoscopy was performed outside the clinic, or surgery was performed immediately. However, the results of this study elucidated the pathologic characteristics and risk factors of GC patients younger than 40 years of age. In addition, in propensity matching, the frequency of *H. pylori* infection is low in the elderly (4.9%); however, this could be misleading, because it was unclear whether the patient had already been treated for the eradication of *H. pylori*, and/or the test itself was lost. Therefore, *H. pylori* eradication is recommended even in patients ≤40 years of age.

Conclusion

Patients ≤40 years of age more often had family histories and *H. pylori* infection compared to patients >40 years, and pathologic findings were more common in SRC. Therefore, more active screening and *H. pylori* eradication are needed even in patients aged ≤40 years.

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References

1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 2018; **68**: 394–424.
2 Jung KW, Won YJ, Kong HJ, Lee ES. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2016. *Cancer Res. Treat.* 2019; **51**: 417–30.
3 Nakamura R, Saikawa Y, Takahashi T *et al.* Retrospective analysis of prognostic outcome of gastric cancer in young patients. *Int. J. Clin. Oncol.* 2011; **16**: 328–34.
4 Dhobi MA, Wani KA, Parray FQ *et al.* Gastric cancer in young patients. *Int. J. Surg. Oncol.* 2013; **2013**: 981654.

5 Isobe Y, Nashimoto A, Akazawa K *et al*. Gastric cancer treatment in Japan: 2008 annual report of the JGCA nationwide registry. *Gastric Cancer*. 2011; **14**: 301–16.
6 Eguchi T, Takahashi Y, Yamagata M, Kasahara M, Fujii M. Gastric cancer in young patients. *J. Am. Coll. Surg.* 1999; **188**: 22–6.
7 Koea JB, Karpeh MS, Brennan MF. Gastric cancer in young patients: demographic, clinicopathological, and prognostic factors in 92 patients. *Ann. Surg. Oncol.* 2000; **7**: 346–51.
8 Isobe T, Hashimoto K, Kizaki J *et al*. Characteristics and prognosis of gastric cancer in young patients. *Oncol. Rep.* 2013; **30**: 43–9.
9 Anderson WF, Camargo MC, Fraumeni JF Jr, Correa P, Rosenberg PS, Rabkin CS. Age-specific trends in incidence of noncardia gastric cancer in US adults. *JAMA*. 2010; **303**: 1723–8.
10 Theuer CP, de Virgilio C, Keese G *et al*. Gastric adenocarcinoma in patients 40 years of age or younger. *Am. J. Surg.* 1996; **172**: 473–6 discussion 6-7.
11 Saito H, Takaya S, Fukumoto Y, Osaki T, Tatebe S, Ikeguchi M. Clinicopathologic characteristics and prognosis of gastric cancer in young patients. *Yonago Acta Med.* 2012; **55**: 57–61.
12 Park HJ, Ahn JY, Jung HY *et al*. Clinical characteristics and outcomes for gastric cancer patients aged 18-30 years. *Gastric Cancer*. 2014; **17**: 649–60.
13 Kim DY, Ryu SY, Kim YJ, Kim SK. Clinicopathological characteristics of gastric carcinoma in young patients. *Langenbecks Arch. Surg.* 2003; **388**: 245–9.
14 Lai JF, Kim S, Li C *et al*. Clinicopathologic characteristics and prognosis for young gastric adenocarcinoma patients after curative resection. *Ann. Surg. Oncol.* 2008; **15**: 1464–9.
15 Al-Refaie WB, Hu CY, Pisters PW, Chang GJ. Gastric adenocarcinoma in young patients: a population-based appraisal. *Ann. Surg. Oncol.* 2011; **18**: 2800–7.
16 Hu B, El Hajj N, Sittler S, Lammert N, Barnes R, Meloni-Ehrig A. Gastric cancer: classification, histology and application of molecular pathology. *J. Gastrointest. Oncol.* 2012; **3**: 251–61.
17 Bosman FT, Carneiro F, Hruban RH, Theise ND. *WHO Classification of Tumours of the Digestive System*. Geneva: World Health Organization, 2010.
18 Yoshikawa K, Maruyama K. Characteristics of gastric cancer invading to the proper muscle layer—with special reference to mortality and cause of death. *Jpn. J. Clin. Oncol.* 1985; **15**: 499–503.
19 Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma–2nd English edition. *Gastric Cancer*. 1998; **1**: 10–24.
20 Ji X, Bu ZD, Yan Y *et al*. The 8th edition of the American Joint Committee on Cancer tumor-node-metastasis staging system for gastric cancer is superior to the 7th edition: results from a Chinese mono-institutional study of 1663 patients. *Gastric Cancer*. 2018; **21**: 643–52.
21 Huang Q, Zou X. Clinicopathology of early gastric carcinoma: an update for pathologists and gastroenterologists. *Gastrointest. Tumors*. 2017; **3**: 115–24.
22 Lee HL, Choi CH, Cheung DY. Do we have enough evidence for expanding the indications of ESD for EGC? *World J. Gastroenterol.* 2011; **17**: 2597–601.
23 Lim JH, Kim J, Kim SG, Chung H. Long-term clinical outcomes of endoscopic vs. surgical resection for early gastric cancer with undifferentiated histology. *Surg. Endosc.* 2019; **33**: 3589–99.
24 Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). *Gastric Cancer*. 2017; **20**: 1–19.
25 Ono H, Yao K, Fujishiro M *et al*. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer. *Dig. Endosc.* 2016; **28**: 3–15.
26 National Cancer Center. *Annual Report of Cancer Statistics in Korea in 2012*. Goyang-si: National Cancer Center, 2014.
27 Kim SJ, Choi CW. Common locations of gastric cancer: review of research from the endoscopic submucosal dissection era. *J. Korean Med. Sci.* 2019; **34**: e231.
28 Kim YI, Kim YW, Choi IJ *et al*. Long-term survival after endoscopic resection versus surgery in early gastric cancers. *Endoscopy*. 2015; **47**: 293–301.
29 Hahn KY, Park CH, Lee YK *et al*. Comparative study between endoscopic submucosal dissection and surgery in patients with early gastric cancer. *Surg. Endosc.* 2018; **32**: 73–86.
30 Correa P. A human model of gastric carcinogenesis. *Cancer Res.* 1988; **48**: 3554–60.
31 Kimura K, Satoh K, Ido K, Taniguchi Y, Takimoto T, Takemoto T. Gastritis in the Japanese stomach. *Scand. J. Gastroenterol. Suppl.* 1996; **214**: 17–20 discussion 1-3.
32 Lee J, Lee MA, Kim IH, Roh SY. Clinical characteristics of young-age onset gastric cancer in Korea. *BMC Gastroenterol.* 2016; **16**: 110.
33 Takatsu Y, Hiki N, Nunobe S *et al*. Clinicopathological features of gastric cancer in young patients. *Gastric Cancer*. 2016; **19**: 472–8.
34 Kim K, Cho Y, Sohn JH *et al*. Clinicopathologic characteristics of early gastric cancer according to specific intragastric location. *BMC Gastroenterol.* 2019; **19**: 24.
35 Shim JH, Song KY, Jeon HM *et al*. Is gastric cancer different in Korea and the United States? Impact of tumor location on prognosis. *Ann. Surg. Oncol.* 2014; **21**: 2332–9.
36 Cormedi MCV, Katayama MLH, Guindalini RSC, Faraj SF, Folgueira M. Survival and prognosis of young adults with gastric cancer. *Clinics*. 2018; **73**: e651s.
37 Liu S, Feng F, Xu G *et al*. Clinicopathological features and prognosis of gastric cancer in young patients. *BMC Cancer*. 2016; **16**: 478.
38 Kim KH, Kim YM, Kim MC, Jung GJ. Analysis of prognostic factors and outcomes of gastric cancer in younger patients: a case control study using propensity score methods. *World J. Gastroenterol.* 2014; **20**: 3369–75.
39 Ji T, Zhou F, Wang J, Zi L. Risk factors for lymph node metastasis of early gastric cancers in patients younger than 40. *Medicine*. 2017; **96**: e7874.
40 Isik M, Caner S, Metin Seker M, Civelek B, Odabas H, Ozdemir N. Gastric adenocarcinoma under the age of 40; more metastatic, less differentiated. *J. BUON.* 2011; **16**: 253–6.
41 Schildberg CW, Croner R, Schellerer V *et al*. Differences in the treatment of young gastric cancer patients: patients under 50 years have better 5-year survival than older patients. *Adv. Med. Sci.* 2012; **57**: 259–65.
42 Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet*. 1984; **1**: 1311–5.
43 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Schistosomes, liver flukes and *Helicobacter pylori*. *IARC Monogr. Eval. Carcinog. Risks Hum.* 1994; **61**: 1–241.
44 Choi IJ, Kook MC, Kim YI *et al*. *Helicobacter pylori* therapy for the prevention of metachronous gastric cancer. *N. Engl. J. Med.* 2018; **378**: 1085–95.
45 Choi IJ, Kim CG, Lee JY *et al*. Family history of gastric cancer and *Helicobacter pylori* treatment. *N. Engl. J. Med.* 2020; **382**: 427–36.
46 Park YM, Kim JH, Baik SJ, Park JJ, Youn YH, Park H. Clinical risk assessment for gastric cancer in asymptomatic population after a health check-up: an individualized consideration of the risk factors. *Medicine*. 2016; **95**: e5351.
47 Asaka M, Kato M, Graham DY. Strategy for eliminating gastric cancer in Japan. *Helicobacter*. 2010; **15**: 486–90.
48 Asaka M. A new approach for elimination of gastric cancer deaths in Japan. *Int. J. Cancer*. 2013; **132**: 1272–6.

Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Figure S1. Absolute standardized difference (ASD) before and after propensity score matching.

Table S1. Baseline characteristics, pathologic findings, and outcomes in young patients ≤40 years of age ($n = 88$).

Table S2. Risk factors of signet ring cell carcinoma in all study subjects ($n = 2307$).

Table S3. Risk factors of recurrence in propensity-matched analysis of 132 patients.